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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,458	08/13/2001	David Wallach	WALLACH=22A	6865

7590 07/26/2005

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,458	WALLACH ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,18-20 and 27-35* is/are pending in the application.

4a) Of the above claim(s) *18-20 and 27-29* is/are withdrawn from consideration.

5)☒ Claim(s) *30-35* is/are allowed.

6)☒ Claim(s) *13, 15 and 16* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 13-16, 18-20, and 27-35 are pending.

2. Claims 18-20 and 27-29 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 10/20/04, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 13 and 15-16 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated polypeptide which is capable of binding to RIP which polypeptide comprises: a RIP-associated protein encoded by a DNA sequence in a clone deposited with Collection Nationale de Culture de Microorganisms under accession number I-2706; a fragment of (a) which binds to RIP and a derivative of (a) or (b) by modification of a functional group which occurs as a side chain or an N- or C-terminal group of one or more amino acid residues thereof without changing one amino acid to another of the twenty commonly-occurring natural amino acids, which derivative binds to RIP, (2) an isolated polypeptide comprising a protein whose amino acid sequence is that of SEQ ID NO: 2, (3) the polypeptide mentioned above comprises the amino acid fragment of a RIP-associated protein (RAP) encoded by a DNA sequence in a in a clone deposited with Collection Nationale de Culture de Microorganisms under accession number I-2706 which binds to RIP; and (4) a composition comprising the polypeptide mentioned above and a pharmaceutically acceptable carrier, **does not** reasonably provide enablement for all isolated polypeptide which is capable of binding to RIP (1) "comprises" any "fragment" of RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Culture de Microorganisms under accession number I-2706 which binds to RIP, (2) any isolated polypeptide comprises any "analog" of an isolated polypeptide which is capable of binding to RIP which polypeptide comprises: a RIP-associated protein encoded by a DNA sequence in a clone deposited with

Collection Nationale de Culture de Microorganisms under accession number I-2706 having no more than ten changes in the amino acid sequence of said polypeptide, each said change being any "deletion", or any "insertion" of an amino acid, which analog binds to RIP, (3) any "derivative" of said "analog" having no more than ten changes in the amino acid sequence of said polypeptide, each said change being any "deletion", or any "insertion" of amino acid by modification of a functional group which occurs as a side chain or an N- or C-terminal group of one or more amino acid residues thereof without changing one amino acid to another of the twenty commonly-occurring natural amino acids, which derivative binds to RIP, (4) any polypeptide which "comprises" any fragment of RIP--associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Culture de Microorganisms under accession number I-2706 which binds to RIP, and (5) a composition comprising *any* "fragment", *any* "analog" or *any* "derivative" mentioned above and a pharmaceutically acceptable carrier for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one polypeptide comprising the amino acid sequence of SEQ ID NO: 2 encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 for blocking Jun kinase induction caused by RIP (See page 86 of the specification). The specification on page 86, line 5-7 discloses that RAP **was incapable** of binding to any of the known intracellular signaling proteins such as MORT-1/FADD, TRAF1, TRAF2, MACH, Mch34, and G1 mentioned above, including the irrelevant control proteins, such as lamin and cyclin D. The specification further discloses the following biological activities (i) RAP is not toxic to cells on its own when overexpressed, (ii) RAP does not protect cells from TNF killing, (iii) RAP does not induce NF-κB on its own, (iv)

RAP does block NF-κB activation by TRADD, RIP and p55 TNF-R and (v) blocks Jun kinase induction caused by RIP (See page 87 of the specification).

The specification does not teach how to make any all isolated polypeptide "comprises" any "fragment" of RIP-associated protein (RAP) because the term "comprises" is open-ended. It expands the "fragment" to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added and whether the resulting polypeptide maintains its structure, much less binding to RIP.

With regard to any analog having no more than ten deletion of amino acid, there is insufficient guidance as to which ten amino acids within the full-length polypeptide of RIP-associated protein (RAP) comprising the amino acid sequence of SEQ ID NO: 2 encoded by the deposited clone to be deleted, and whether the resulting polypeptide maintains its structure and still binds to RIP. With regard to any analog having no more than ten insertion of amino acid, there is insufficient guidance as to which ten amino acids to be inserted and where within the full-length polypeptide of RIP-associated protein (RAP) comprising the amino acid sequence of SEQ ID NO: 2 to be inserted, let alone the resulting polypeptide maintains its structure, much less exhibits substantially the same or higher biological activity as the RAP protein.

Given the unlimited number of RAP analog, there is insufficient working example demonstrating any analog or derivative binds to RIP and modulate (inhibit or stimulate) which RIP activity in any intracellular pathways mediated by RIP.

Given the RIP-associated protein (RAP) has 522 amino acids, it is unpredictable which ten amino acid within the 522 amino acids of RAP be deletion, or insertion that the resulting RAP analog maintains its structure and still binds to RIP.

Skolnick et al teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

Whisstock et al teach prediction of protein function from sequence is difficult, messy partly because function is a fuzzy and multi-faceted concept and partly because small or even no changes in amino acid seuqence are capatible with large changes in funciton (see entire document, page 335, in particular). Whisstock et al conclude that "predictions of protein functions are useful but no substitute for workin the laboratory. Indications from theory may indict, but only experimentatal evidence can convict" (see page 335, conclusions, in particular).

Lin *et al*, of record, teach a variety of signals induce activation of NF-kappaB (See page 5899, column 1, first full paragraph, in particular) and RIP plays a structural rather than an enzymatic role in the TNFα response (See page 5899, column 2, last paragraph, in particular).

Kim *et at*, of record, teach a single amino acid change from D to A at position 324 of RIP (RIPD324A) activates NF-kappaB activation while ectopic expression of proapoptotic C-terminal fragment of RIP inhibited TNF-induced NF-kappaB activation (Abstract, in particular).

Ito et al teach protein-protein interaction using yeast two hybrid screening is useful for large scale approaches to map the comprehensive protein net work, however, various limitations are inherent to the two-hybrid system, especially there are many false positive or biologically meaningless signals (see page 4573, col. 1, second full paragraph, in particular). On the other hand, a number of false negative also evident (see page 4573, col. 1, third full paragraph, in particular). Ito et al teach the success of screening totally depends o the design of the baits: some can reproduce all of the previously reported interactions whereas others not at all (see page 4573, col. 1, last paragraph, in particular). Given the RAP protein encoded by the deposited clone has 522 amino acids, it is unpredictable which ten amino acid within the 522 amino acids of RAP be deletion, or insertion that the resulting RAP analog maintains its structure and still binds to RIP. Since the polypeptide "comprises" any fragment of RAP, any polypeptide comprises any analog mentioned above are not enabled, it follows that the derivative of said fragment and analog are not enabled. It also follows that the composition comprising any polypeptide comprises any "fragment" or any "analog" and derivative thereof mentioned above are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 5/3/05 have been fully considered but are not found persuasive.

Applicants' position is that the examiner objects to the language that the polypeptide "comprises" a fragment of (a) which binds to RIP. Applicant's position is that regardless of the presence of amino acids upstream and downstream of the fragment, the claim requires that the fragment itself be capable of binding to RIP. Once it is clear that the fragment retains the ability to bind to RIP, there is no reason to believe that addition of residues upstream and downstream thereof will prevent the full polypeptide from binding. Further, the preamble requires the entire polypeptide also be capable of binding to RIP. With respect to analogs, the invention can be practiced without undue or unreasonable experimentation.

In response, the term "comprising" is open-ended. It extends the fragment to include additional residues upstream and down stream of the peptide. Without guidance for the amino acids to be added, the length of the fragment is uncertain. With respect to analog, the specification has not identified which ten amino acids within the full-length polypeptide of RAP be deleted, or inserted that the resulting RAP analog maintains its structure and still binds to RIP. Further, merely binding does not equal to any biological function. The specification discloses the analogs, fragments and derivatives thereof, which *may be* used to inhibit the signaling process, or, more specifically, the inflammation cell-cytotoxicity, cell-survival processes, when desired. There is insufficient in vivo working example showing the peptide fragment and analog of RIP associated protein in involved in any inflammatory process or cell-survival processes. Whisstock et al teach prediction of protein function from sequence is difficult, messy partly because function is a fuzzy and multi-faceted concept and partly because small or even no changes in amino acid seuqence are capatible with large changes in funciton (see entire document, page 335, in particular). Whisstock et al conclude that "predictions of protein functions are useful but no substitute for workin the laboratory. Indications from theory may indict, but only experimentatal evidence can convict" (see page 335, conclusions, in particular). For these reasons, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

6. Claims 13, 15 and 16 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) "comprises" any "fragment" of RIP-associated protein (RAP) encoded by a DNA sequence in a clone

deposited with Collection Nationale de Culture de Microorganisms under accession number I-2706 which binds to RIP, (2) any isolated polypeptide comprises any "analog" of an isolated polypeptide which is capable of binding to RIP which polypeptide comprises: a RIP-associated protein encoded by a DNA sequence in a clone deposited with Collection Nationale de Culture de Microorganisms under accession number I-2706 having no more than ten changes in the amino acid sequence of said polypeptide, each said change being any "deletion", or any "insertion" of an amino acid, which analog binds to RIP, (3) any "derivative" of said "analog" having no more than ten changes in the amino acid sequence of said polypeptide, each said change being any "deletion", or any "insertion" of amino acid by modification of a functional group which occurs as a side chain or an N- or C-terminal group of one or more amino acid residues thereof without changing one amino acid to another of the twenty commonly-occurring natural amino acids, which derivative binds to RIP, (4) any polypeptide which "comprises" any fragment of RIP--associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Culture de Microorganisms under accession number I-2706 which binds to RIP, and (5) a composition comprising *any* "fragment", *any* "analog" or *any* "derivative" mentioned above and a pharmaceutically acceptable carrier for treating *any* disease.

The specification discloses only one polypeptide comprising the amino acid sequence of SEQ ID NO: 2 encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganisms under accession number I-2706 (See page 86 of the specification). The specification on page 86, line 5-7 discloses that RAP **was incapable** of binding to any of the known intracellular signaling proteins such as MORT-1/FADD, TRAF1, TRAF2, MACH, Mch34, and G1 mentioned above, including the irrelevant control proteins, such as lamin and cyclin D. The specification further discloses the following biological activities (i) RAP is not toxic to cells on its own when overexpressed, (ii) RAP does not protect cells from TNF killing, (iii) RAP does not induce NF-κB on its own, (iv) RAP does block NF-κB activation by TRADD, RIP and p55 TNF-R and (v) blocks Jun kinase induction caused by RIP (See page 87 of the specification).

With the exception of the specific polypeptide mentioned above, there is insufficient written description about the structure associated with function of all polypeptide "comprises" any fragment of RIP-associated protein (RAP) without the amino acid sequence. Further, the term "comprises" is open-ended. It expands the "fragment" to include additional amino acids at either or both ends. There is inadequate written description about the amino acids to be added.

With regard to polypeptide comprises any analog of RIP-associated protein (RAP) having no more than ten changes in the amino acid sequence of said polypeptide, each said change being any deletion, or any insertion of an amino acid, there is inadequate written description about which ten amino acids within the full length RIP-associated protein (RAP) that has 522 amino acids to be deleted, which amino acids to be inserted and where within the 522 amino acids to be inserted such that the resulting polypeptide maintains its structure and function. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification as-filed does not provide adequate written description support for any polypeptide comprises any fragment or "analog" having no more than ten changes in the amino acid sequence of said polypeptide, each said change being any deletion, or any insertion of an amino acid without the amino acid sequence. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. Until the structure of the polypeptide "comprises" any fragment, any "analog" and "derivative" of said analog of RIP-associated protein (RAP) have been identified and described, the specification merely asks one skilled in the art to go figure for themselves what the claimed polypeptide "comprises" any "fragment", any "analog" and "derivative" of RIP-associated protein look like.

Finally, the specification discloses only one polypeptide comprising SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of polypeptide such as polypeptide "comprises" any fragment, any analog and derivative of RAP to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 5/3/05 have been fully considered but are not found persuasive.

Applicants' position is that the description in the specification is very similar to the description which appears in the present specification. The present claim 13 is drawn to a method of use that includes an analog of RAP having effectively at least 95% identity with the sequence of RAP has the ability to bind RIP. Moreover, the procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity was conceded as being conventional in the art. It is apparent that if the single species disclosed is representative of the genus and an assay is present for identifying the members of the variants that are capable of the specified functionality, the written description requirement is met.

In response, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed fragment and analogs without the amino acid sequence and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of binding. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The amino acid sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The specification has not disclosed which amino acids within the RAP encoded by the deposited DNA to be substituted, deleted, or added such that the RAP fragment and analog RAP may serve as an inhibitor and which amino acid substitution, deletion, or addition may serve as an inhibitor or augmentor of the cell-survival pathway.

Finally, the specification discloses only one polypeptide comprising SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of polypeptide such as polypeptide "comprises" any fragment, any analog and derivative of RAP to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

7. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. Claims 30-35 are allowed.

9. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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July 22, 2005

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